REMARKS

Claims 1-4, 6-10, 12-15, 19-22, and 24 are pending in the application. Claims 17-18 and 25 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claims 5, 11, 16, and 23 were previously cancelled. Claims 1, 6, 7, 12, 19, and 24 are presently amended.

These claims have been amended, withdrawn, or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim amended, withdrawn, or cancelled for any reason. Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Applicants wish to thank Examiner Dutt for the courtesies extended to the Applicant's Representative and inventor Dr. Tully in the personal interview held July 30, 2009.

I. Claim Amendments

Discussed during the personal interview with the Examiner on July 30, 2009[1] was the possibility of claim amendments to more clearly define the screening methods, especially with respect to the requirements for selecting a test compound. While the Applicants believe that these amendments are not necessary – and indicated so in their Statement of Substance mailed on August 21, 2009 – they have amended the claims to simplify terminology and to expedite prosecution.

A. *Claims 1-4, 6-10, 19-22, and 24*

The four determinations of indicator activity underlying the requirements for selecting a test compound have now been amended so that they are presented as consecutive recitations with common terminology.[2] This rearrangement provides a clearer view of the similarities and differences among the four determinations; it does not, however, prescribe a particular order for carrying out the determinations. This

[1] See last page of Examiner Interview Summary, mailed August 4, 2009.
[2] See steps b) through e) in amended claim 1; steps c) through f) in amended claim 19.

rearrangement also provides a simple point of reference to more concisely define the requirements for selecting a test compound in these claims.

B. ***Claims 7, 12-15, and 19***

The steps of assessing CREB-depending gene expression have also been amended so that they too are presented as consecutive recitations with common terminology. This rearrangement has been made for clarity and simplicity; it does not, however, prescribe a particular order for carrying out assessments. This rearrangement also provides a simple point of reference to more concisely define the requirements for identifying candidate cognitive enhancer compounds and confirmed candidate cognitive enhancer compounds. These amended recitations are also present in claims 7 and 19.

II. Rejections Under 35 U.S.C. § 103(a)

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish a *prima facie* case of obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations.[3] Fourth, if an obviousness rejection is based on a combination of prior art references, the Examiner must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test").[4]

Following the Supreme Court's decision in *KSR v. Teleflex*,[5] this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way so as to become inconsistent with the Court's flexible approach of *Graham v. Deere*.[6] The prong must still be applied, however, because it captures the important insight that "a

[3] *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).
[4] *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).
[5] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).
[6] *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007).

patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."[7]

A. ***Claims 1-4, 6-10, 19-22, and 24***

The Examiner has maintained the rejection of claims 1, 3-4, 6-7, and 9-10 over Sheriff et al. ("Sheriff") in view of Herzog et al. ("Herzog"). The Examiner has also maintained the rejection of claims 2, 8, 19-22, and 24 over Sheriff in view of Herzog and further in view of Barad et al. ("Barad").

Applicants respectfully traverse for the reasons stated in their Reply Under 37 C.F.R. § 1.116, dated July 17, 2008; their Reply & Amendment Under 37 C.F. R § 1.111, dated December 29, 2008, and their Reply & Amendment Under C.F.R. § 1.116, dated August 21, 2009, which are hereby incorporated by reference. Applicants also traverse for the following additional reasons:

1. Sheriff does not teach the selecting steps recited in claims 1-4, 6-10, 19-22, and 24.

Claims 1-4 and 6-10 all include selecting step g), which requires that the indicator activity determined in step d) is not significantly different than the indicator activity determined in step e). Step d) recites "determining indicator activity in said host cells which have been contacted with test compound alone," and step e) recites "determining indicator activity in said host cells which have not been contacted with said test compound or said CREB function stimulating agent."

Likewise, claims 19-22 and 24 all include selecting step h), which requires that the indicator activity determined in step e) is not significantly different than the indicator activity determined in step f). Step e) recites "determining indicator activity in said host cells which have been contacted with test compound alone," and step f) recites "determining indicator activity in said host cells which have not been contacted with said test compound or said CREB function stimulating agent."

In other words, selecting steps g) and h) each require that CRE-indicator activity does not differ significantly in cells treated with a test compound versus cells that have been treated with no compounds.

[7] *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007).

The Examiner has asserted that Figure 5 of Sheriff discloses this requirement:

> Furthermore, Sheriff et al. demonstrate that the luciferase activity in control cells treated with NPY but not with forskolin is not significantly different from the activity elicited by control cells that are not treated with either forskolin or with NPY (Figure 5, 1st and 2nd bar).
> 5.26.09 OA at page 5

The Applicants respectfully contend that this assertion is erroneous for at least two reasons:[8] First, and contrary to the Examiner's assertion, Sheriff does not demonstrate that the 1st and 2nd bars in Figure 5 are not statistically different. Figure 5 and its legend are reproduced here:

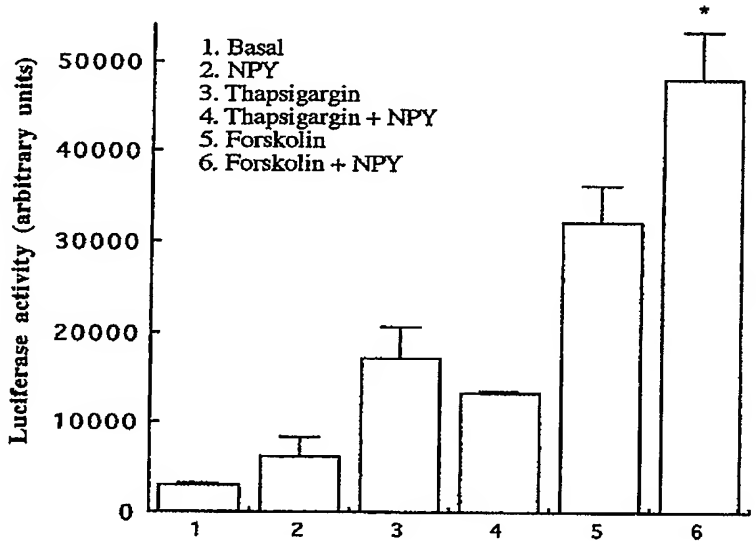


Fig. 5. NPY augments forskolin-stimulated luciferase activity but had no effect on thapsigargin-induced luciferase activity in SK-N-BE2 cells. After transfection, the cells were treated stimulated with forskolin (10 μM) or thapsigargin (10μM), and NPY (100 nM) was added 5 minutes later. Luciferase activity was monitored after 4 h incubation. Values are the mean + S.E. of three parallel determinations. Similar values were obtained in other two experiments. **Additive effect of NPY with thapsigargin or forskolin was compared with thapsigargin- or forskolin-stimulated luciferase activity. *P = 0.007 by Student's t-test.**

The text highlighted in bold reveals that the only statistical comparisons performed here were between bars 5 and 6 (for which there is a significant difference) and between bars 3 and 4 (for which there is not a significant difference).

[8] At least some of these contentions were raised at the personal interview with the Examiner on July 30, 2009.

No statistical analysis (Student's *t*-test) was performed for bars 1 and 2. The Examiner's interpretation of and reliance on Figure 5 is in error, and the present rejection must be withdrawn for this reason alone.

2. Sheriff explicitly contravenes the selecting steps recited in claims 1-4, 6-10, 19-22, and 24.

As depicted in the previous section, the 1st and 2nd bars of Figure 5 actually *do* appear different, in contrast to the Examiner's assertion. Moreover, this apparent difference is explicitly corroborated by the statistical analysis of data presented in Figure 4A of Sheriff. Figure 4A and its legend are reproduced here:

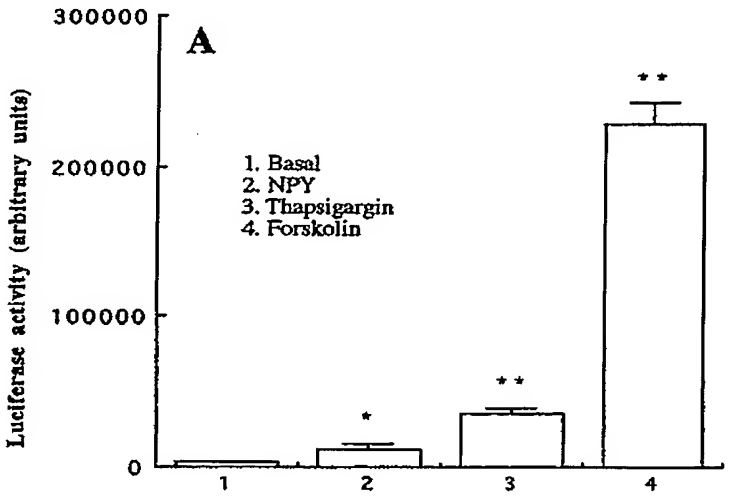


Fig. 4. . . . Cells were transfected with PGL2 basic vector containing hCRF-luciferase fusion gene (A) After 36 hours, the cells were stimulated with NPY (100 nM), thapsigargin (10μM) or forskolin (10 μM) for 4 hr. Values shown here are the means ± S.E. Three to four experiments done in duplicate. **NPY-, thapsigargin- or forskolin-treated groups were compared with basal. *$P \leq 0.05$ *or* ** $P \leq 0.0001$ by Student's *t*-test.**

The text highlighted in bold reveals that a statistical comparison was performed here on bars 1 and 2. And the results reveal that there is a significant difference in luciferase activity between these two groups, corroborating the visual comparison made in Figure 5. Sheriff does not teach or suggest – and in fact, contravenes – the requirements for the selecting steps of claims 1-4, 6-10, 19-22, and 24, and this deficiency is not overcome by Herzog or Barad.

For all the reasons set forth here, Applicants assert that claims 1-4, 6-10, 19-22, and 24 are not obvious in over Sheriff, whether in view of Herzog or in view of Herzog

and further in view of Barad. Accordingly, Applicants respectfully request that the Examiner reconsider and withdrawn the rejection under 35 U.S.C. § 103(a).

B. ***Claims 12-15.***

The Examiner has maintained the rejection of claims 12 and 14-15 over Sheriff in view of Herzog. The Examiner has also maintained the rejection of claim 13 over Sheriff in view of Herzog and further in view of Barad.

Applicants respectfully traverse for the reasons stated in their Reply Under 37 C.F.R. § 1.116, dated July 17, 2008; their Reply & Amendment Under 37 C.F. R § 1.111, dated December 29, 2008, and their Reply & Amendment Under C.F.R. § 1.116, dated August 21, 2009, which are hereby incorporated by reference. Applicants also traverse for the following additional reasons:

1. Sheriff does not teach or suggest the identifying steps recited in claims 12-15.

Among the recited requirements for identifying step 2) in claims 12-15 is that the cells of neural origin contacted in step b) show significantly more CREB-dependent gene expression than the cells of neural origin contacted in step c). In particular, step b) requires "assessing endogenous CREB-dependent gene expression in said cells of neural origin which have been contacted with said cognitive enhancer compound and with said CREB function stimulating agent" and step c) requires "assessing endogenous CREB-dependent gene expression in said cells of neural origin which have been contacted with said CREB function stimulating agent alone."

In other words, identifying step 2) requires that endogenous CREB-dependent gene expression is significantly increased in neural cells treated with a test compound and a CREB function stimulating agent relative to neural cells treated with the CREB function stimulating agent alone. The Examiner has asserted that Figure 6 of Sheriff renders this requirement obvious in view of the knowledge of one of ordinary skill in the art:

> Sheriff et al. also teach contacting cells (not transfected) of the neuroblastoma cell line with NPY and forskolin, and assess the expression of endogenous gene containing CRE (Y1 receptor). The reference further teaches that although NPY treatment increases the Y1 mRNA expression, forskolin in more potent in upregulating Y1 receptor

> message, when compared to untreated controls (page 314, Section 3.6 of Results, Figure 6).
>
> Sheriff et al. do not teach the addition of both NPY and forskolin to neuroblastoma cells for the analysis of gene expression.
>
> However, in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the reference and to treat the cells with both NPY (as the candidate compound) and forskolin. Each of these compounds has been taught in the prior art to augment CREB dependent gene expression and increase Y1 mRNA
>
> 5.26.09 OA at page 5

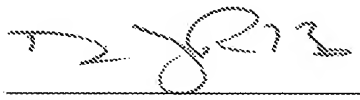
Assuming for the sake of argument only that one skilled in the art *would* treat these cells with both forskolin and NPY, Sheriff still does not teach or suggest the requirement in step 2) that this combined treatment be significantly greater than treatment with the CREB function stimulating agent alone. In other words, Sheriff has no bearing on whether such a comparison, even if carried out, would reveal a statistically significant increase. Sheriff does not teach or suggest such a possibility, and Herzog or Barad does not overcome this deficiency.

For all the reasons set forth here, Applicants assert that claims 12-15 are not obvious over Sheriff, whether in view of Herzog or in view of Herzog and further in view of Barad. Accordingly, Applicants respectfully request that the Examiner reconsider and withdrawn the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,



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